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| EXAMINER | |
|---|---|
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| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/920,571 | LASKEN ET AL. | |
| | Examiner | Art Unit | |
| | Teresa E Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 July 2004 and 17 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5-9,11-15,20-25,27,29-59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9, 11-15,20-25,27,29-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *14032003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This office action is in response to amendments filed June 16, 2004 and October 17, 2004. Claims 1, 5-9, 11-15, 20-25, 27 and 29-61 were pending. Applicants amended claims 1, 39, 54 and cancelled claims 60 and 64-68. Claims 1, 5-9, 11-15, 20-25, 27, 29-60 and 61 are pending and will be examined.

2. Applicants are notified that claim identifier "previously amended" (in claims 29-31, 34, 35, 50, 56, 59 and 61) is incorrect, and "previously presented" should be used instead. For the sake of advancing the prosecution the amendments are considered, but the claim indicators need to be corrected.

3. Applicants' amendments and claim cancellations overcame the rejection of claims 39, 54 and 60 under 35 U.S.C. 112, second paragraph. The terminal disclaimer filed June 16, 2003, obviated the obviousness-type double patenting rejection of claims 1, 5-9, 11-15, 20-25, 27 and 29-61 over claims of the U.S. Patent No. 6,323,009.

4. All of the other rejections are maintained for reasons given in the "Response to Arguments" section below.

### *Terminal Disclaimer*

5. The terminal disclaimer filed on June 16, 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the U.S. Patent No. 6,323,009 B1 has been reviewed and is accepted. The terminal disclaimer has been recorded.

### *Information Disclosure Statement*

6. The information disclosure statement (IDS) submitted on March 14, 2003 was filed after the mailing date of the non-final rejection on December 20, 2002. The submission is in compliance

with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

***Response to Arguments***

7. Applicant's arguments filed June 16, 2003 have been fully considered but they are not persuasive.

A) Regarding the rejection of claim 1 under 35 U.S.C. 112, second paragraph, Applicants state that the claim has been amended to remove the terms "naturally occurring dNTP different from the foregoing", "dNTP analog", "dNTP having a universal base", however, they are still present in claim 1, therefore the rejection is maintained.

B) Regarding the rejection of claim 50 under 35 U.S.C. 112, second paragraph, Applicants state that the claim has been amended to change "said 3'-terminal nucleotide" and "said primer" to "the 3'-terminal nucleotide" and "the primer". However, "said" and "the" have the same meaning. Further, Applicants state that these terms are defined by the fact that claim 1 recite a primer which has a 3'-terminus. However, claim 1 recites multiple primers (line 3), therefore it is not clear which one of these primers claim 50 refers to.

The rejection is maintained.

C) Regarding the rejection of claims 56 and 61 under 35 U.S.C. 112, second paragraph, Applicants state that the claim has been amended to remove the phrase "such as" in claim 56. However, it is still there (line 3, "such as Taq,...").

The rejection is maintained.

D) Regarding the rejection of claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54, 60 and 62 over Lizardi-1 (U.S. Patent No. 5,854,033) and Lizardi-2 (U.S. Patent No. 6,124,120), Applicants argue the following:

a) Neither reference teaches or suggests using dNTPs that render the resulting TS-DNA resistant to exonucleases.

b) Lizardi-1 does not teach using multiple primers with an ATC, but only with the TS-DNA.

c) Lizardi-1 teaches producing an ATC from an open circle probe by ligation, and ligation is not part of the method of claim 1.

d) There is no motivation to combine the Lizardi-1 and Lizardi-2 references, since Lizardi-2 teaches amplification of linear sequences and duplexes, not circular nucleic acids, therefore there is no motivation for one of skill in the art to combine a method of amplification of linear duplex DNA with a method of amplification of circular DNA.

Regarding a), claim 1 does not require the use of nuclease-resistant dNTPs, since the dNTPs listed in the Markush group are not required to be nuclease resistant. Therefore, if only dTTP is used in the amplification, the resulting product will not be nuclease resistant. Lizardi-1 teaches amplification using DNA polymerase, therefore it inherently teaches multiple dNTPs. Lizardi-1 also teaches nucleotide analogs such as radioactive nucleotides (col. 21, lines 22-25) and fluorescent nucleotides (col. 11, lines 2-5). Lizardi-2 teaches amplification, therefore it inherently teaches multiple dNTPs , and also specifically teaches multiple dNTPS (col. 25, lines 57, 58). Further, Lizardi-1 (U.S. Patent No. 5,854,033), teaches primers which include modified nucleotides to make them exonuclease-resistant (col. 10, lines 24-28; col. 13, lines 27-31). Therefore, Lizardi-1 suggests using nuclease-resistant nucleotides to make the amplification products nuclease resistant.

Regarding b), the secondary and tertiary primers of Lizardi-1 used to amplify TS-DNA, are complementary to ATC (col. 25, lines 36-49). If a primer is complementary to TS-DNA, which contains multiple copies of ATC, then it is also complementary to ATC. Therefore, Lizardi-1 teaches multiple primers complementary to ATC.

Regarding c), the limitation that ATC is not obtained by ligation is not a limitation of claim 1. Therefore, any circular nucleic acid can be used, no matter how it was obtained. Further, Applicants define ATCs as either double or single-stranded: "Amplification target circles (ATCs) useful in the processes of the present invention are circular DNA or RNA molecules, either single or double stranded, including DNA-RNA hybrid molecules generally containing between 40 to 10,000 nucleotides. However, it is expected that there will be no upper limit to the size of the ATC." (page 15, lines 4-8).

Regarding d), Applicants question the combination of references on the grounds that amplification of duplex DNA is different from amplification of single stranded DNA. In fact, for anyone familiar with nucleic acid amplification, there is no such distinction. Duplex DNA amplification proceeds through separate amplification of each of the single strands, and, in fact, strand separation is necessary for PCR, for example. Fig. 4 of Lizardi-2 shows amplification of denatured strands of duplex DNA.

Applicants admit that Lizardi-2 teaches the same process as Lizardi-1: "In effect, Lizardi-2 is doing the same kind of process as Lizardi-1 in that Lizardi-2 uses multiple primers for each strand of a duplex target while Lizardi-1 is using multiple primers on the single stranded TS-DNA product of RCA. However, neither reference (either alone or in combination) uses multiple primers on an ATC itself and neither suggests doing so." (page 13 of the response, first paragraph). Since both Lizardi-1 and Lizardi-2 teach multiple primers, and Lizardi-2 teaches random primers, the combination of references suggests claim 1.

The rejections are maintained.

E) Regarding the rejection of claims 8 and 9 over Lizardi-1 (U.S. Patent No. 5,854,033), Lizardi-2 (U.S. Patent No. 6,124,120) and Sorge et al., Applicants did not provide any arguments.

The rejection is maintained.

F) Regarding the rejection of claim 15 over Lizardi-1 (U.S. Patent No. 5,854,033) and Lizardi-2 (U.S. Patent No. 6,124,120), Applicants argue that amendment to claim 1 made this claim non-obvious over the combination of these references. The arguments regarding the combination of references were addressed above.

The rejection is maintained.

G) Regarding the rejection of claims 32, 41, 46, 47 and 59 over Lizardi-1 (U.S. Patent No. 5,854,033), Lizardi-2 (U.S. Patent No. 6,124,120) and Skerra, Applicants argue that incorporation of the limitation of dNTPs which make the TS-DNA resistant to nuclease obviates this rejection. This argument was addressed above.

The rejections are maintained.

H) Regarding the rejection of claims 30, 34 and 43 over Lizardi-1 (U.S. Patent No. 5,854,033), Lizardi-2 (U.S. Patent No. 6,124,120) and Cummins, Applicants argue that the rejection is an oversight because these claims were cancelled. Claims 30, 34 and 43 are listed as pending claims.

The rejection is maintained.

I) Regarding the rejection of claims 55 and 56 over Lizardi-1 (U.S. Patent No. 5,854,033), Lizardi-2 (U.S. Patent No. 6,124,120) and Sorge et al., Applicants argue that amendment to claim 1 made these claims non-obvious over the combination of references. The arguments regarding claim 1 were addressed above.

The rejection is maintained.

J) Regarding the rejection of claims 55 and 56 over Lizardi-1 (U.S. Patent No. 5,854,033), Lizardi-2 (U.S. Patent No. 6,124,120), Applicants argue that amendment to claim 1 made these

claims non-obvious over the combination of references. The arguments regarding claim 1 were addressed above.

The rejection is maintained.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), referred to as Lizardi-1, and Lizardi-2 (U.S. Patent No. 6,124,120).

A) Lizardi-1 teaches amplification of circular DNA molecule by a rolling circle method. The rolling circle amplification (RCA) involves hybridization of a primer to amplification target circle (ATC) followed by amplification using strand-displacing DNA polymerase (column 19, lines 20-31), resulting in a DNA molecule with multiple repeats of the ATC, usually referred to as tandem sequences DNA (TS-DNA).

In one embodiment of the amplification, strand displacement cascade amplification, (SDCA), secondary and tertiary primers are used, with sequences complementary to the ATC (col. 25, lines 36-49). The SDCA can be performed simultaneously with RCA, resulting in exponential amplification (col. 28, lines 8-18; col. 26, lines 61-66).

The primers are from 10 to 35 nucleotides long (col. 10, line 14).

The primers can contain a region at the 5'-end which is non-complementary to the ATC (col. 10, lines 16-22).

The ATC is a circular, single-stranded DNA molecule, of 40 to 1,000 nucleotides (col. 9, lines 25-29.

The ATC can be derived from a single-stranded bacteriophage (col. 35, lines 50-59).

Radioactive nucleotides can be used in the amplification (col. 21, lines 22-25).

Primers may include modified nucleotides to make them exonuclease-resistant. The phophorothioate nucleotides can be positioned at the 5'-end of the primer (col. 10, lines 24-28; col. 13, lines 27-31).

Fluorescence-labeled nucleotides can be used (col. 11, lines 2-5).

The DNA polymerases to be used include: bacteriophage $\phi$ 29 DNA polymerase, phage M2 DNA polymerase, VENT DNA polymerase, Klenow fragment of DNA polymerase I, T5 DNA polymerase, PRD1 DNA polymerase, T4 DNA polymerase holoenzyme (col. 17, lines 66-67, col. 18, lines 1-11).

Lizardi-1 teaches oligonucleotides attached to solid support, including glass (col. 14, lines 34-43, 65-67; col. 15, lines 1-10).

B) Lizardi-1 does not teach random primers, linear DNA, duplex DNA with or without nicks, DNA larger than 10,000 nucleotides or DNA with unknown sequence.

C) Lizardi-2 teaches multiple strand displacement amplification (MSDA) method, in which multiple primers are used to amplify DNA strand of interest (col. 2, lines 25-53). The method can be used to amplify any target nucleic acid (col. 5, lines 21-25), including whole genomic DNA using random primers (col. 3, lines 6-10). The DNA molecules to be amplified can be very long, on the order of 50,000 nucleotides (col. 2, lines 64-67).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have included random primers and DNA molecules of Lizardi-2 in the methods of

Lizardi-1. The motivation to do so would have been that random primers allowed for amplification of unknown DNA sequences, and using double-stranded DNA targets broadened the range of amplifiable target DNAs.

10. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above, and further in view of Sorge et al. (U.S. Patent No. 5,599,921).

A) Claim 8 is drawn to the multiple primers being hexamers, and claim 9 to multiple primers being octamers.

B) Lizardi-1 or Lizardi-2 do not teach hexamers or octamers as primers.

C) Sorge et al. teach families of oligonucleotides from 6 to 8 bp long for use as primers, with sequences substantially complementary to the target DNA (col. 4, lines 27-33; col. 12, lines 8-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used primers of Sorge et al. in the amplification method of Lizardi-1 and Lizardi-2. The motivation to do so would have been hexamers and octamers were used to construct of libraries of primers in large quantities for use in amplification reactions.

11. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 12 and 13 above.

A) Claim 15 is drawn to denaturing two strands of a duplex DNA circle in the amplification process.

B) Neither Lizardi-1 nor Lizardi-2 teach denaturation step of the duplex DNA circle.

It was well known and common knowledge in the art that amplification reaction involving primers and double-stranded DNA required separation of the two strands, usually achieved by

denaturation. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have addded a denaturation step to the amplification reaction when amplifying double-stranded DNA.

12. Claims 32, 41, 46, 47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1, 38 and 44 above, and further in view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554, 1992).

A) Claims 32 and 41 are drawn to a polymerase with 3'-> 5' exonuclease activity, claim 46 to a modified nucleotide being a 3'-terminal nucleotide, claim 47 to the modified nucleotide being a phosphorotioate nucleotide and claim 59 to the use of a mixture of primers sensitive to and resistant to exonuclease activity.

B) Neither Lizardi-1 nor Lizardi-2 teach primers resistant to 3'-> 5' exonuclease activity, the resistance being conferred by a phosphorothioate nucleotide at the 3'-end of the primer or the use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction.

C) Skerra teaches that incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'-> 5' exonuclease activity of DNA polymerases such as Vent and Pfu. The reference also teaches use of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction (page 3553, Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used primers of Skerra with phosphorothioate nucleotides at the 3'-end in the amplification method of Lizardi-1 and Lizardi-2. The motivation to do so would have been that the 3'-end phosphorothioate nucleotide rendered the primers resistant to 3'-> 5' exonuclease activity the polymerase used in the reaction, resulting in an improved yield of the amplification product.

13. Claims 30, 34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1, 26 and 43 above, and further in view of Cummins et al. (Biochemistry, vol. 35, p. 8734-8741, 1996).

A) Claim 30 is drawn to the nuclease activity being due to endonuclease, claims 34 and 43 are drawn to the nuclease activity due to contaminating nuclease.

B) Neither Lizardi-1 nor Lizardi-2 teach nucleotides conferring resistance to endonuclease activity due to contaminating nucleases.

C) Cummins et al. teach oligonucleotides containing nucleotides with phosphorodithioate linkages which are resistant to nucleases in nuclear and cytoplasmic extracts (Abstract; Figure 1; page 8738, paragraphs 2-5; page 8739; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used phosphorodithioate-modified nucleotides of Cummins et al. in the method of Lizardi-1 and Lizardi-2. The motivation to do so, expressly provided by Cummins et al., would have been that these nucleotides conferred resistance to oligonucleotides present in nuclear and cytoplasmic extracts and in human serum.

14. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above and further in view of Sorge et al. (U.S. Patent No. 5,556,722).

A) Claim 55 is drawn to DNA polymerase without the 3'->5' exonuclease activity, and claim 56 to specific DNA polymerases not exhibiting this activity (e.g. Taq, Tfl, etc.)

B) Neither Lizardi-1 nor Lizardi-2 teach DNA polymerases without the 3'->5' exonuclease activity (exo(-)).

C) Sorge et al. teaches Taq DNA polymerase which lacks 3'->5' exonuclease activity (col. 5, lines 30-67; col. 6, lines 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used exo(-) Taq DNA polymerase in the method of Lizardi-1. The motivation to do so, expressly provided by Sorge et al., would have been that Taq polymerase was highly processive.

15. Claims 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above.

A) Claim 57 is drawn to the DNA polymerase being a reverse transcriptase and claim 58 to the ATC being RNA and the DNA polymerase being a reverse transcriptase.

B) Neither Lizardi-1 nor Lizardi-2 teach RNA targets or reverse transcriptase.

C) Lizardi-2 teaches that a target DNA can be any nucleic acid (col. 5, lines 21-25) and amplification of cDNA obtained from mRNA (col. 21, lines 14-20).

D) It was well known and common knowledge in the art at the time of the invention that cDNA was obtained from mRNA using reverse transcriptase.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have included RNA targets of Lizardi-2 in the amplification method of Lizardi-1. The motivation to do so would have been that RNA amplification provided a measure of gene expression in cells.

***Conclusion***

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
February 11, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER